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Minutes

Agricultural Biotechnology Research Advisory Committee

Working Group on Risk Assessment and Environmental Safety

August 25, 1992

Document No. 92-WG-01

U.S. DEPARTMENT OF AGRICULTURE
Agricultural Biotechnology Research Advisory Committee

Working Group on Risk Assessment
Minutes of Meeting
August 25, 1992

The Agricultural Biotechnology Research Advisory Committee (ABRAC) Working Group on Risk Assessment (henceforth referred to as the Working Group) met on August 25, 1992, in the Georgetown Room of Rosslyn Westpark Hotel in Arlington, Virginia. Dr. David Andow chaired the meeting. The meeting was open to the public and had been announced in the Federal Register.

Members of the Working Group in attendance were Dr. David Andow, Dr. Anne Vidaver, Dr. Ronald Sederoff, and Dr. Edward Bruggemann. Expert guests included Dr. Peggy Lemaux, Dr. Raymond Rodriguez, Dr. James Cook, and Dr. Tom Givnish. Also attending was Dr. Sue Tolin, a former member of the ABRAC. Persons in attendance from the Office of Agricultural Biotechnology (OAB) were Alvin L. Young, Daniel Jones, Maryln K. Cordle, Marti Asner, and Barry Stone. Persons from USDA's Animal Plant and Health Inspection Service (APHIS) who attended were Mr. Terry Medley, Dr. John Payne, Dr. Sally McCammon, Dr. Michael Schechtman, Dr. Jim Lackey, Dr. Jim White, and Dr. Arnold Foudin. Others who attended are listed in Appendix A.

Call to Order and Preliminaries

Dr. Andow called the meeting to order at 9:04 a.m. He introduced the members of the Working Group, as well as the experts who had been invited to comment on the subjects to be discussed.

Dr. Andow then asked if the meeting agenda met with the Working Group's approval. Dr. Vidaver moved that the agenda be approved, and Dr. Sederoff seconded the motion. The agenda was approved unanimously.

Dr. Andow then explained that the Working Group had visited with some of the APHIS staff in early July to discuss which aspects of field trials and oversight of experiments involving genetically modified organisms should be included on the agenda. After conferring with the APHIS staff, the Working Group had decided to discuss proposed performance standards for two specific crops, generic standards, specific risk assessment issues, and special concerns.

Dr. Andow then introduced Mr. Terry Medley of APHIS, who reviewed his agency's experience with field trials and oversight.

Review of Field Trial Experience and Oversight

Mr. Medley said that since 1987, APHIS has issued permits for the field testing of transgenic plants that are developed with genetic material from known plant pests. He noted that the statutory definition of plant pests with which the agency must work is very broad. The definition includes any organism that could inflict direct or indirect injury, disease, or damage to a plant.

When evaluating field test proposals, APHIS focuses not on the technique used to insert the genetic material into the plant pests, but on the source of the material. In addition, the evaluation is not scale dependent. APHIS also evaluates the host plant, and the new trait(s) that the genetic material will add to the plant.

Between October 1, 1987, and August 3, 1992, APHIS issued 318 permits for field testing. Initially, these permits focused on proposed tests of plants bred for insect resistance, virus resistance, and herbicide tolerance; tomatoes and tobacco were the predominant plant types. However, since then the range of plant characteristics and plant types has expanded considerably. In the current fiscal year, potatoes are close to surpassing tomatoes as the predominant plant type being tested, followed by corn, soybeans, and cotton. Moreover, APHIS is issuing single permits that cover field testing at multiple sites in multiple states.

Mr. Medley said that the average approval time from application submission to the issuance of a permit is 92 days.

Mr. Medley then introduced Dr. Michael Schechtman, who discussed APHIS's proposed performance standards for field tests involving transgencic potatoes.

Transgenic Potatoes

Dr. Schechtman said that permits have been issued for some 50 field tests on transgenic potatoes. The breakdown for these tests is as follows:

1. Insect-resistant (Colorado potato beetle resistance) potatoes: 11 tests

2. Metabolic changes: 12 tests

3. Herbicide tolerance: 2 tests

4. Virus resistance: 24 tests

5. Bacterial, fungal disease resistance: 12 tests

6. Marker genes: 3 tests

Of the 50 permits, 28 have been issued to industrial applicants, 6 have been issued to universities, and 16 have been issued to scientists from USDA's Agricultural Research Service (ARS).

Dr. Schechtman then outlined the important features of potato biology, noting that the conclusion of any proposal evaluation is based on what is known about the basic properties of the potato. He added that any modification should not change those basic properties.

Dr. Schechtman said that the 23 trials conducted to date indicated that:

1. There was no unexpected survival after one year at any of the test sites.

2. None of the modified potatoes had been observed to move out of the test sites.

3. No *Agrobacterium* infection occurred.

4. There were no unexpected phenotypes outside the normal range of variation of potato.

5. About half the Russet Burbank marker gene transformants had properties and qualities that were equal to the parental variety.

6. The levels of marker gene expression were stably maintained through three generations.

7. Traits were passed more efficiently to progeny if the transgenic potato parent was female rather than male.

Dr. Schechtman said that these results were the basis for APHIS's proposed performance standards for transgenic potatoes. He asked the Working Group whether the proposed standards omitted any risk assessment issues.

Dr. Sederoff asked whether the method of introducing the DNA being considered by APHIS was restricted to *Agrobacterium* only. Dr. Schechtman explained that *Agrobacterium* is the vector that APHIS is most familiar with, but not the only one it regulates. Dr. Sederoff then asked whether APHIS also considers direct DNA transfer methods; Mr. Medley responded that plants that contain DNA that has been transferred directly is not considered regulated material. Dr. Sederoff asked if that was true no matter what the transferred gene was; Mr. Medley said that was

something the Working Group should discuss. Dr. Sederoff pointed out that the Proposed Guidelines for Research Involving Planned Introduction into the Environment of Genetically Modified Organisms (henceforth referred to as the Guidelines) address this issue.

Dr. Sederoff then asked what level of plant pest material contained in a plant concerns APHIS. Dr. John Payne replied that the legal definition is somewhat at odds with the level that may concern APHIS from a scientific viewpoint. The legal definition indicates that any plant pest sequence, no matter at how low a level, is subject to regulation by APHIS. Dr. Sederoff said that might be inappropriate.

Dr. Andow cautioned the Working Group not to focus on the definition of a plant pest, which already has been specified by statute. He reminded the Working Group that APHIS was asking whether it is possible to create a performance standard.

Dr. Sederoff said he thought that performance standards regarding containment were acceptable, but he was not sure whether standards for other areas would be appropriate.

Dr. Payne said that traits, not the method of transferring those traits, need to be looked at.

Dr. Bruggemann asked for a definition of the term "horizontal transfer," and whether there has been actual evidence of such transfers taking place. Dr. Schechtman said that horizontal transfer is movement of genetic material by any means other than normal, sexual transfer. He said there is indirect evidence that such transfers may have occurred, but there is no evidence in the scientific literature that functional genes are actively transferred from plants to associated microorganisms.

Dr. Bruggemann then asked if anything is known about the effects of super-infecting viruses. Dr. Payne said that the proposed performance standards refer to a set of sequences involving endemic viruses.

Dr. Tolin then asked how APHIS had compiled its list of endemic viruses. Dr. White said that the list of viruses had been developed with State officials, and that lists were available for most States.

Dr. Tolin noted that interactions among such viruses had been observed occurring naturally 10 years before, and that the virus that forms from such interactions lasts only one generation. Such interactions have occurred in tobacco, tomatoes, and wheat; Dr. Tolin said she did not know of such interactions involving potatoes. However, as Dr. Bruggemann pointed out, such interactions could be inferred.

Dr. Rodriguez asked how APHIS planned to use the performance standards. Mr. Medley replied that USDA was discussing the ultimate use of the standards.

Dr. Vidaver noted that many of the performance standards were indistinguishable from common standard practice. She suggested that handling of the plant after the field test be considered, and that the standards' failure to address post-test use implied that the plants were too dangerous for consumption even by animals. Dr. Payne explained that the U.S. Food and Drug Administration (FDA) deals with the food uses of such plants.

Dr. Andow then asked the four experts to comment on the performance standards for potatoes.

Dr. Rodriguez said that while APHIS has done an excellent job of putting together the proposed standards, current regulations are not based on sound scientific principles; specifically, too many transgenic plants are subject to regulation. Instead of focusing on a "regulated article," APHIS should focus on traits, he suggested.

Mr. Medley responded by warning against assuming that the performance standards would be used as part of a mandatory permit and review process. He reiterated that the ultimate use of the standards has not been determined.

Dr. Rodriguez asked how many of the field test applications were exempted from the review process. Mr. Medley replied that there had been two petitions for such exemptions — one involving tomatoes, the other involving squash — and that APHIS had issued an opinion that the petitions in question did not involve regulated articles.

Dr. Rodriguez then said he would like to see the performance standards used as a checklist which, if followed by investigators, would exempt those investigators' proposals from the permit process. Dr. McCammon said that rationales for such exemptions are needed.

Dr. Cook said he felt that the performance standards reflected overconcern with microbes vis-a-vis macrobes. He also objected to the double-packaging standard, pointing out that a potato deemed safe through the application of preceding standards should not be subject to the same packaging as a potato deemed unsafe. Dr. Lamaux said that when field tests were just beginning, such caution was justified, but that over the past 5½ years, enough knowledge had been accumulated to provide answers to many questions. She cautioned against assessing process instead of risk.

Dr. Givnish asked if APHIS had addressed the possibility that birds could transport potato berries over long distances. Dr. Lackey said while such dispersal is possible, there is no record of sustainable volunteers resulting from such dispersal.

Dr. Givnish then said that the performance standards contain no explicit discussion of potential environmental impacts, and suggested dealing with the nature of the introduced trait.

Dr. Andow then asked members of the public to comment on the proposed performance standards.

Dr. Mellon said that basing the performance standards on the concept of a "regulated article" is inadequate because such a basis does not cover the full range of environmental risks. She said a new statute is needed to address the entire range of risks resulting from work with transgenic plants. She suggested that scientists look for experiences that enable future procedural streamlining in order to avoid wasting precious time and resources on low-risk plants. She also said 49 percent of those who had been allowed to perform field tests had not submitted the required reports to USDA, and that those investigators who did submit report relied too much on gross observations. While performance standards are theoretically a good idea, more information should be made available, she concluded.

Dr. Goldburg agreed with Dr. Mellon that the current regulatory trigger is not scientifically defensible, and that there is some room for streamlining of the permit process. She expressed concern that the standards lack sufficient detail.

Dr. Tolin said that the performance standards could be made more generic, and that they should include more information about basic biological properties.

Dr. Bruggemann asked why the Working Group should not discuss how the standards would be used. He also asked whether the conclusions on the potato standards resulted from casual observations. Dr. Payne responded that the observations were carefully thought out and timed.

Dr. Givnish asked if the female parent passed traits more efficiently than males was due to a cytoplasmically inherited factor. Dr. Schechtman said that evidence did not indicate such a factor, but the researcher who had reached that conclusion was still investigating why it had occurred.

After a lunch break, Dr. Andow asked Dr. McCammon to discuss proposed performance standards for transgenic corn and generic performance standards, as well as traits of special concern.

Transgenic Corn/Generic Standards/Traits of Special Concern

Dr. McCammon began her presentation by outlining the characteristics of genetic traits at three levels of fitness.

Traits increasing fitness give a plant a selective advantage vis-a-vis other plants and remain in the gene pool. Examples are disease resistance and insect resistance.

Traits influencing fitness in particular environments give a plant a selective advantage in special circumstances and may be lost from the gene pool. An example is herbicide tolerance.

Traits reducing fitness give a plant selective disadvantages and are lost from the gene pool. An example is male sterility. Such traits are of concern to APHIS.

Dr. McCammon went on to say that APHIS issued most permits for field testing of corn plants last year and this year, mainly for herbicide tolerance, marker genes, and resistance to viruses and insects.

With respect to generic standards, Dr. McCammon suggested the following possibilities:

- Stable integration;
- Incapable of generating virions;
- Control over handling and biological fate of the plant material; and
- No significant impacts on flora or fauna.

Dr. Givnish said the "no significant impacts" standard was too vague; Dr. Vidaver said that the idea of "standard agricultural practices" also might be considered vague, but was accepted in the agricultural research community.

Dr. Vidaver then said that some of the examples of traits of special concern presented by APHIS merited further discussion. Dr. Andow said that more background materials are needed for such a discussion.

Dr. Andow went on to say that traits of special concern do exist; the question is whether such traits can be defined in an inclusionary manner, not an exclusionary manner.

Dr. Cook questioned the need for special security measures, such as double boxing, during scale-up and development if an organism met applicable performance standards at small-scale. Dr. Payne replied that the intent of the performance standard is to

establish conditions for a reasonable presumption of safety. If an organism is not fully characterized or if it is being tested in the environment for the first time, he said, there might be reason for due care in subsequent handling of the organism.

Dr. Andow pointed out that expanding the performance standards on risk to include environmental risks is important when moving from small-scale to large-scale production of plants developed through biotechnology. He said that under such circumstances, geographic specifications would be needed, and that generic determinations would be much tougher to make than crop-specific determinations would be.

Dr Givnish asked that the possibility of seed dispersal by birds capable of long-distance movement be added to the list of traits of special concern.

Dr. Andow then invited APHIS staffers to discuss specific risk assessment issues.

Specific Risk Assessment Issues

Dr. Lackey discussed isolation distances. He said that isolation distances were part of a larger set of safeguards intended to minimize uncontrolled gene movement away from plantings of transgenic plants. Safeguards would include: shipping material to and from the planting site; accounting and recordkeeping for all material used and disposed of; knowledge of the biology of the plant; conduct of the planting, especially with regard to pollen-mediated gene flow and mechanical movement of plant parts; remedial measures for accidents or unanticipated events; and termination of the planting.

Dr. Lackey have examples for potato, corn, and soybean proposed isolation distances in the draft performance standards, how they fit into the safeguard scheme, and how they are based on scientific literature and on the use of certified seed distances as recommended by scientific experts.

Dr. Givnish observed that seed certification distances are established mainly to prevent economically significant contamination of the seed crop by pollen from outside the plot. He saw that as a different issue from preventing gene escape. He also pointed out the importance of knowing the behavior of local pollinators.

Dr. White discussed the experimental use of exotic pests and disease agents as challenge organisms. He explained that researchers could legally circumvent regulations that control importation of whole virus particles by importing part of the virus, and then reassembling the parts in the United States to

form a whole virus. These reassembled viruses are inserted into plants — under contained conditions — to confer disease resistance on the plants.

APHIS has approved two such experiments; Dr. White asked whether APHIS should approve more of these experiments, whether importation should be permitted, and (if so) under what conditions.

Dr. Vidaver noted that other scientific organizations are grappling with these questions, and Dr. Tolin said this issue is a quarantine issue, not a biotechnology issue. After considerable discussion, Dr. Andow suggested that a wider group of scientists is needed to advise APHIS on this issue. Dr. Vidaver suggested that APHIS obtain that advice by publishing a request for comment in the Federal Register.

Dr. Payne discussed organism identification. He said that some applicants for field testing permits were not identifying organisms properly, and that greater support for taxonomic work in risk assessment is needed. The Working Group supported Dr. Payne's position.

Dr. Andow then asked Dr. Ann Lichens-Park to discuss negative effects data.

Negative Effects Data

Dr. Lichens-Park said that negative effects data are important because they are at the center of a dilemma that could threaten USDA's risk-based regulation of biotechnology.

In an experiment, negative effects may have one of two results: a negative result, in which the hypothesis is not supported; or neutral effects, in which nothing unusual happens. Either way, negative effects data often are not published; they are either forgotten or become part of the unwritten lore of the scientific community, even though the data are potentially useful information.

The National Biological Impact Assessment Program (NBIAP) of CSRS is attempting to find a way to make negative effects data more accessible. The NBIAP is developing a biomonitoring database to facilitate safe experimental design and regulatory compliance. The database is updated continually and will be distributed to the public on CD-ROM.

Dr. Lichens-Park then posed several questions to the Working Group:

1. Does all agricultural biotechnology need to be subjected to formal risk assessments if the available information indicates there is little risk?

2. Who should conduct such risk assessments?

3. Has enough effort been put into risk management?

4. Who should oversee risk management? How should results from the end of field tests be handled?

5. How should negative or neutral results be collected?

6. Who should have access to negative effects data?

Dr. Andow said that USDA should answer the questions regarding who should do what. He said that not all agricultural biotechnology research should be subject to risk assessment and management; the question is how to decide what should and should not be subjected to those processes.

Dr. Givnish said that it would be difficult to publish negative effects data because pseudo-replication might arise; a scientist cannot assume that an experiment on one organism would lead to the same results when performed on another organism. A meta-experiment that includes many different kinds of organisms, or a cross-referencing database could address that issue, he said.

Dr. Cook said that when data do not fit a hypothesis, the hypothesis has to be changed, at which point publication does occur.

Dr. Andow said that information from negative effects data can serve as a model for future analysis. Dr. Lamaux suggested that it be made clear in a formal way that such data are useful.

Dr. Andow then suggested that the Working Group try to reach a conclusion regarding the day's discussions and discuss future meetings.

Conclusions and Future Meetings

Dr. Andow began by saying that he sensed the Working Group agreed that the APHIS performance standards approach is scientifically valid if the definition of a regulated article is excluded. He said he also sensed that the Working Group agreed with APHIS's philosophical approach.

Dr. Andow then asked the four experts to write reports on the specific issued raised on the proposed performance standards for potatoes, corn, and soybeans, and possibly also the generic

standards. Those reports should be sent to Dr. Young within the next three weeks for incorporation into the minutes [attached as Appendix B]. Dr. Young would send the reports to Dr. Andow, who would summarize them and ask for comments on the summary from the Working Group. After making the changes requested by the Working Group, the comments will be submitted to Mr. Medley. [*Note*: This request was modified during the ABRAC meeting on August 26, 1992.]

Dr. Vidaver asked if the Working Group could agree on whether generic or crop-specific performance standards should be used. Dr. Sederoff suggested that the containment standards be made crop-specific; the traits of concern could be dealt with in the Guidelines.

With regard to future issues for the Working Group to address, Dr. Givnish suggested that more attention be given to environmental effects. Dr. Lamaux suggested that attention be paid to how to identify traits of special concern. Dr. Cook suggested that ABRAC broaden its purview in this area to include microorganisms.

Dr. Sederoff said that while it is very important to consider ecological effects, they should be considered with respect to unmodified organisms. He said that he feared that genetically modified organisms are being held to a higher standard than are unmodified organisms.

Dr. Bruggemann said that the ABRAC might not be the group to deal with the issue of importing exotic plant viruses, and suggested that the American Phytopathological Society might be a better group to deal with it.

Dr. Andow summarized the Working Group's conclusions based on the day's discussions. With respect to APHIS's generic performance standards, the Working Group agreed that the standard specifying that the introduced genetic material should be stably integrated into the genome of the transgenic plant, and the standard specifying that the introduced genetic construct should be incapable of generating infectious viruses or virions are applicable generically.

The Working Group disagreed to some extent as to whether the standard which specified the need for applicant control over the location and biological fate of the transgenic plant and tissues derived from the plant could be applied generically. The Working Group disagreed considerably as to whether the standard which specified the need to conduct an experiment so that it has no significant impact on flora or fauna was applicable generically.

The Working Group agreed that the issue of exotic virus importation should be addressed by other experts. The issues of

genetically modified biocontrol agents, environmental effects assessments, and traits of special concern would need to be crop-specific.

Dr. Bruggemann moved that the meeting be adjourned. Dr. Sederoff seconded the motion. The meeting adjourned at 4:33 p.m.

Approved:

Susan McCullough

SUSAN McCULLOUGH
Rapporteur

Daniel Jones

DANIEL JONES
Editor

Alvin L. Young

ALVIN YOUNG
Executive Secretary

DAVID ANDOW
Chair

APPENDIX A

LIST OF VISITORS
UNITED STATES DEPARTMENT OF AGRICULTURE
AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE
WORKING GROUP ON RISK ASSESSMENT
Meeting of August 25, 1992

Ann Lichens-Park, Cooperative State Research Service, USDA
Arthur Kelman, Cooperative State Research Service, USDA
Margriet Caswell, Economic Research Service, USDA
Kelly Day, Economic Research Service, USDA
Cassandra Klotz, Economic Research Service, USDA

Margaret Mellon, National Wildlife Federation
Rebecca Goldburg, National Resources Defense Council
Ken Reid, Food Chemical News
Jeanette Glover Glew, U.S. Food and Drug Administration
Roger Jennings, British Embassy

Lisa Zannoni, Office of the Secretary, USDA
Jay Blowers, Cooperative State Research Service, USDA
Barbara Masters, Food Safety and Inspection Service, USDA
Oto Urban, Food Safety and Inspection Service, USDA
Nathan Bauer, Food Safety and Inspection Service, USDA

Jo Randall, ICI Seeds
Frank Serdy, Monsanto Company
Alan Raul, U.S. Department of Agriculture
Terry Stone, Monsanto Company
Frank Tang, Animal and Plant Health Inspection Service, USDA

Peter Dunn, Purdue University
Bharat Patel, Food Safety and Inspection Service, USDA
Mike Carsky, Animal and Plant Health Inspection Service, USDA
Larry McDaniel, American Phytopathological Society
Jim White, Animal and Plant Health Inspection Service, USDA

David Heron, Animal and Plant Health Inspection Service, USDA
Sally Van Wert, Animal and Plant Health Inspection Service, USDA
Chuck Eby, Fleishman-Hilliard
Shirlene Matten, U.S. Environmental Protection Agency
Pat Basu, Food Safety and Inspection Service, USDA
Thelma Tennant, Cooperative State Research Service, USDA

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Appendix B

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September 10, 1992

Dr. David Andow
ABRAC Working Group on Risk Assessment
University of Minnesota
Department of Entomology
St. Paul, MN 55108-6125

Dear David:

RE: Field testing of transgenic plants

If it is a given that the concept of 'regulated article' will remain in place, then the following comments apply. In principle, performance standards can be justified, just as they are for nongenetically-engineered plants. The performance standards, as written, particularly the specific ones for crops, are very much like design standards rather than performance standards. The generic standards come closer to performance standards. Neither are clearly based on risk. There is no discussion of biosafety levels relative to risk, even working with a plant pest or what is believed to be a plant pest. In the specific performance standards for specific crops, there is some recognition of categorization of safety concern with specific organisms, but it would be extremely helpful if this could be articulated as an area needing development and further discussion. The problem remains in all these discussions that it is the source of the genetic material that is the basis for oversight.

Let me begin with generic performance standards. There needs to be some preamble in that the safety issue is that a plant pathogen or plant pest is of concern when introduced into field trials. This is the case whether the organism is engineered or not, and whether the organism is or is not a biological control organism.

Analysis of safety is not necessarily related to stability of a trait. It is ideal to stably integrate a trait into a transgenic plant, but lack of stability is not a safety factor per se. One must look at the trait or phenotype, itself, to evaluate the safety concern. One could even argue that having an unstable trait is the least likely to present a safety concern because of lack of probably effective reproduction and dissemination.

It is appropriate to indicate that plants derived via any of the new biotechnology should be free of introduced viable cells which are plant pathogens or pests. It is reasonable to say that the introduced genetic construct should be incapable of generating infectious viruses or virions not endemic in the area in which the tests will be performed. The safety concern is of introducing new types of viruses or virions, or in transmissible, infectious agents by any means, such as genomic complementation, resulting in viruses that have potential to cause damage or harm which are not known to be present in the test site areas or in the United States, including territories. The experiments should be conducted to minimize safety concerns, if any, with respect to dissemination of the transgenic plant material. The plants should be considered the equivalent of unmodified plants, unless there are clear safety concerns. Due to the interest in these types of experiments, particular attention should be paid to monitoring the transgenic plants for significant adverse affects on flora, fauna, and/or the environment, based on the expected phenotype. Similarly, a mitigation plan should be considered before initiating the experiment, should an unanticipated, significant, adverse effect be detected.

Since negative data seem to be the norm, relative to unexpected effects, and the acquisition of such data and dissemination of the data are of concern, the following could be included: to demonstrate lack of safety concern with respect to the introduced phenotype, a periodic monitoring system needs to be in place, with defined attributes that will be examined. These should be considered relative to the phenotype of the transgenic plant and commensurate with safety concern of similar phenotypes of nongenetically-engineered plants.

Performance standards for field testing of specific crops.

The safety issue with respect to recipient potato plants is irrespective of the recipient characteristics. These performance standards should be that the resulting phenotype should not be able to directly or indirectly injure or cause disease or damage to other plants or parts thereof. That is, the origin of a construct is not a safety issue per se. In order to minimize the probability that a plant pest attribute will occur in the resulting transgenic plant, certain precautionary measures should be considered. These include a) using so-called disarmed Ti plasmids, b) using noncoding cis-acting regulatory DNA elements, c) using virus protein genes of viruses endemic to a region, if appropriate, or to the United States and using virus anti-sense genes of common viruses endemic to a region or the United States. If plant pest components are used in the construction of a transgenic plant, monitoring for its presence in a new construct should be part of the experimental

protocol. Such protocol should include, where appropriate, latent or nonsymptomatic infections. Without reference to a phenotype or trait, the performance standard for field testing of potato plants should be the same as unmodified potato plants.

The only addition, because transgenic plants are regulated articles, should apply to monitoring of the trait in question, and shipment and use of the material.

The same general comments apply to any of the crops listed. That is, the objectives should be that there is no new plant pest risk as a result of genetic manipulation.

A general statement accompanying all the performance standards, whether or not generic or specific should be of the order that persons should consult with state or land-grant or federal authorities on best practices for a crop in the region or site in which the tests are to be conducted.

A potential exclusion for consideration under 'regulated article' is the following, derived from the letter to C. Boyden Gray. Oversight of transgenic plants is excluded where: 1) the recipient plant lacks the characteristics of a plant pest; and 2) the plant results from the addition of genetic material from a donor which is a plant pest where: a) the genetic basis of the mechanisms by which the donor causes injury, disease or other damage are well characterized and the full genomic complement for those mechanisms is not transferred to the recipient plant; or b) the genetic basis of the mechanisms by which the donor causes injury, disease or other damage are not well characterized and less than the necessary part of the donor's genome has been transferred to the recipient plant that would result in reconstitution of a complete and functional genome of an exotic readily transmissible, infectious agent by genomic complementation. Such an exclusion would eliminate consideration of plants due to process alone.

Some categorization of safety concerns with traits is appropriate. It could be analogous to the FDA document, for example as in Science (1992). That is, properties that are well known, even if not fully characterized, are generally of low safety concern. For example, the FDA points out that almost all the proteins introduced by recombinant DNA techniques are well known, and they are not known to result in toxic effects in vertebrates (at least). APHIS could construct some similar type of language. That is, the USDA, either through ABRAC or APHIS should have oversight functions at the federal level for properties that are not familiar in the recipient plants that are known to be toxic to vertebrates or other beneficial organisms. Again, the FDA Science article illustrates some of

these groups of proteins, carbohydrates, fats and oils that would be of safety concern. I would include those suggested by APHIS illustrative of 'special concern'. These include potent pharmaceutical and therapeutic agents, immunologically reactive proteins and hydrocarbon polymers, and toxins or derived toxins. In having oversight of such types of experiments, properties of the recipients certainly must be considered, not only in context with the environment (soil, air, water), but particularly to the fauna that might ordinarily encounter such recipient plants. Public discussion of the type of oversight, commensurate with safety concern, is at issue, not that the experiments should not be conducted. Unless there is some clear selective advantage, I would not have a great concern for transmission of the trait to other plants; of the several hundred plant experiments conducted thus far, transmissibility of the trait under experimental conditions can only be accomplished with poor management technique of such a nature that would not be considered standard experimental practice. This is an area in which scale-up could be a safety concern. It is in this type of an area that I would agree with Margaret Mellon, who indicated at our last meeting "don't waste time and effort on low-risk experiments".

Importation of exotic plant viruses

In consultation with 4 virologists, we do not see any significant risk in the importation of non-infectious portions of viral genomes. Risk comes when these portions are recombined with other viral nucleic acids to produce an infectious hybrid or 'wild-type' virus. If APHIS would regulate the importation of partial genomic sequences, it would only hinder the development of nucleic acid based detection procedures in other legitimate uses.

APHIS should require permits for the construction and use of infectious, exotic, viral genomes. Information used to construct the virus could come from a published nucleic acid sequence or from partial genomic clones. Permit requirements for the use of these 'synthetic' infectious constructs should be no more stringent than those required for the non-recombinant strains of the virus.

With respect to what are important biological attributes of the virus and host plant (exotic plant viruses): most biological factors of an infectious particle that relate to the epidemiology of the virus are important. It would be difficult to single out any particular attribute.

Given the reality of 'regulated articles', I have no problem with a notification scheme, as long as it is fair and equitable, and based on real as opposed to perceived safety concerns. Again, the FDA article provides guidance, as well as traditional agriculture. It is important to recognize that there is a safety concern with all agricultural products; few are of moderate to high safety concern.

Sincerely,

Anne

Anne K. Vidaver
Professor & Head

UNIVERSITY OF CALIFORNIA AT BERKELEY
COOPERATIVE EXTENSION

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September 11, 1992

Dr. Alvin Young
Director Office of Agricultural Biotechnology
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Washington, D.C. 20250

Dear Dr. Young:

This memorandum is written to summarize my thoughts on the Risk Assessment Working Group meeting held in Washington D.C. on August 25, 1992. We were asked to share written comments on questions raised by the Animal and Plant Health Inspection Service in the memorandum of August 8, 1992 written to you by Mr. Medley. Because of my strong commitment to the advancement of biotechnology as a powerful tool to address agricultural problems, I am concerned about several general issues relating to the regulatory process. Although my extensive biotechnology experience allows me to respond knowledgeably to many of the issues raised in the memorandum, I find it unconscionable to discuss the mechanics of the regulatory process without first adequately addressing certain basic scientific issues central to determination of the need for regulation.

Since my exposure to the political processes that govern the development of regulatory policy is minimal, I am not aware of potential political ramifications of my comments. I intend that these comments be used as constructive criticism and I offer them to Mr. Medley, the ABRAC and you as matters of great concern to me as a scientist and consumer. I look forward to continued interaction on these issues.

THE REGULATORY PROCESS AS OUTLINED IN MR. MEDLEY'S MEMORANDUM IS STILL PROCESS-BASED, NOT RISK-BASED.

As emphasized by Dr. Rodriguez and other scientists and environmentalists present at the meeting, the definition of a "regulated article" as implemented by APHIS, is not scientifically sound and is inappropriate for useful regulation and protection of the public and the environment. Scientifically sound assessment of the safety of agricultural products should involve only the potential for risk and not the means by which the organism is modified. The essential question is whether the product poses a substantial risk. The danger in looking at every genetic engineering experiment utilizing a sequence from a plant pest is that the real issues of risk and safety could be lost in the mental entanglement generated by examining safe experiments. A

case in point was the fruitless discussion at our working group meeting as to whether a single nucleotide from a virus constituted a "regulated article". The debate of such questions will lead to the disenchantment of both the scientific community and the public.

Additionally, the present APHIS system does not regulate plants of potential risk, that derive from the use of genes that are not plant pest-based or from, for instance, wide-species crosses. The latter group of plants have been safely field-tested for years using standard research and plant breeding practices. Researchers can now choose to genetically engineer plants with a trait of potential human risk that does not derive from a plant pest, e.g. snake venom toxin or a natural plant insecticide, such as cyanoglycoside. The expression of these genes could be controlled by "non-pest" regulatory sequences. Regulation of the field testing of these experiments would not fall within APHIS' regulatory authority. Depending on the nature of the plant, it is my understanding that various aspects of the human health risks of such products would be regulated under Health and Human Services through the Public Health Service, the Centers for Disease Control, the NIH Office of Recombinant DNA Activities, the Food and Drug Administration, and the Environmental Protection Agency. The oversight process for products bearing such potential risk must be orchestrated in such a way that suitable regulatory umbrellas are easily identifiable and that, where necessary, the appropriate agencies communicate and exchange information.

THE DEVELOPMENT OF GUIDANCE PRINCIPLES FOR IDENTIFYING AND MITIGATING THE RISKS POSED BY AGRICULTURAL CROPS HAS NEEDED AND CONTINUES TO NEED THE DIRECT INVOLVEMENT OF THE EXPERT SCIENTIFIC COMMUNITY

If the focus of the regulatory process becomes risk-based rather than process-based, common sense will dictate seeking the guidance of the scientific community in determining what plants warrant scrutiny. This assessment of risk should be irrespective of the means of introduction or the origin of the trait, *i.e.* whether the nucleotide sequence derives from a plant virus, a bacterium or a mammalian cell. Questions of safety and environmental concern regarding plant pests or other introduced traits, that cannot be addressed by the existing, extensive body of scientific literature, should be addressed by rigorous experimentation (*e.g.* 1989 National Research Council Report, "Field Testing Genetically Modified Organisms: Framework for Decisions").

I am aware that using the assessment of risk as the obligatory requirement for regulation transcends the current APHIS scheme. In the absence of a strict risk-based approach to new product assessment, however, I believe that lapses in the adequate protection of consumers and the public and unwarranted barriers to technological advancement could occur. Environmental assessments on material that bears insignificant risk to public safety and the environment are a waste of time and money and a hindrance to the examination of materials that do pose potential risk. Scientifically based answers to the questions put forward in Mr. Medley's memorandum are appropriate for the determination of the appropriate methodology for regulation. From my viewpoint as a scientific expert and a potential consumer, however, these are not the questions of primary importance for improving regulation of agricul

tural biotechnology. The real issues are what the regulatory process should target for scrutiny and who determines risk. After only brief exposure to how the current regulatory process works, it strikes me that the regulators rather than regulatory needs are driving the process. In my opinion, to protect adequately the public and the environment, the consideration of the inherent risk of a product should dictate the formulation of the appropriate regulatory structures, not the existing structures themselves.

The charge put forth to us as scientific experts was to respond to the questions regarding performance-based standards raised in Mr. Medley's memorandum. Although afforded the opportunity of replying to these issues via written comments, I maintain that the opinions of four scientific experts, regardless of their experience and expertise, are not adequate to formulate the scientific strategy for risk assessment. I think that rigorous scientific answers to the questions raised about risk assessment in Mr. Medley's memorandum are of paramount importance to the future of agricultural biotechnology. They should be addressed in a manner that is commensurate with their importance. In a recent *Science* article (1992, 257:1031), the Food and Drug Administration outlined a strategy to involve industrial and academic scientists more intimately in the decision-making process. The plan is to bring together a group of accomplished scientist to advise the agency on emerging scientific and technical matters and to serve as a liaison with the outside scientific community. This board would be in addition to the numerous scientific and clinical review groups already in use by the FDA for evaluation of drugs. This seems an effective mechanism for addressing the issues raised in Mr. Medley's memorandum. Such a scientific panel should be allowed to set its own scientific agenda and to address the issue of risk assessment, unencumbered by the constraints of the current regulatory framework.

SPECIFIC COMMENTS ON QUESTIONS RAISED IN MR. MEDLEY'S MEMORANDUM

In considering my responses to the questions raised in Mr. Medley's memorandum, please bear in mind the grave reservations outlined above. Although I have not studied the 1989 NRC Report mentioned previously in depth, it strikes me that many of the questions raised by Mr. Medley are addressed in that document.

PERFORMANCE STANDARDS

1.) Can the performance standard approach be justified scientifically?
Assuming that the type of risks deserving review are carefully selected, that the appropriate criteria are used to assess the extent of risk, and that the relevant products are identified for scrutiny, I believe that a performance-based approach can be used. I think that the history of safe conduct in field testing materials derived from wide-species crosses demonstrates that such approaches will work. As was stressed in the 1989 NRC Report, the wealth of information that has been generated to date in field testing should provide the scientific information to justify such an approach.

2.) Should performance standards be tailored specifically to individual crops?
The specific question to be addressed will determine whether generic standards or specialized standards are appropriate. Issues of pollen survival and dissemination may need to be addressed in each crop species, whereas the disposal of materials following the growing season may be dealt with in a more generalized manner. Basic principles of plant breeding illustrate that the particular question to be answered should dictate the appropriate control measures.

3.) What type of data would confirm that the presumption of safety was correct?
The confirmatory data should be derived, as it is for any good scientific experiment, with rigor and the appropriate statistical analyses. In the context of APHIS' current responsibilities, each pressing question relating to *bonafide* plant pest risks, *e.g.* environmental, food safety, *etc.*, can be identified and the appropriate scientific methodology outlined and carried out. Many questions relating to risk can and will be answered in the normal process of carrying out a scientific experiment, without the need for formal regulatory intervention.

TRAITS OF SPECIAL CONCERN

1.) Can criteria be developed for determining what traits should be of greatest concern?
I think that development of inclusive and exclusive guidelines, based on historically effective plant breeding principles, can be developed for assessment of risk. As implied earlier, the National Research Council did this already. They brought together a wide variety of scientific experts with diverse backgrounds and allowed them to come up with such guidelines. APHIS might supplement this guidance with a series of tailored questions that would lead the researcher to the appropriate oversight avenue. In a recent article entitled "Federal Oversight of Genetically Modified Plants" (*Bio/Technology, 1992, 10:967-971*), the authors state that "Scientifically rational schemes for distinguishing between proposed field experiments that need federal regulatory scrutiny and those that do not have been (previously) published (*references*)...and they focus on the characteristics of the modified plant and ask scientifically relevant questions about our familiarity with the modified plant: about the plant's ability to survive, disperse, reproduce and hybridize with crops or wild or weedy plants and about our ability to confine the plants to the test site." I believe that the information contained in the referenced documents should provide an appropriate starting point for developing such criteria.

2.) What characteristics of the plant's biology will be of relevance in assessing potential risks?
I believe that the 1989 NRC Report provides a useful protocol for addressing this issue.

IMPORTATION OF EXOTIC PLANT VIRUSES

1.) What criteria should be used in evaluating the risks associated with the importation of portions of viral genomes?
Historically, I believe that there has been a safe history of transportation of human pathogens in the United States with minimal regulatory burden. It is my impression that this safety has resulted from standard safety practices of researchers and the Public Health Service. I would emphasize that exchange of biotechnological reagents among laboratories internationally is

essential for sustaining basic research and technological innovation.

2) What biological attributes of the virus and host plant will be necessary to safeguard the health of other plants?

This question has too many ramifications to be answered adequately without lengthy scientific debate by experts.

I hope you will find my specific comments helpful. I request that the scientific experts be afforded the opportunity to review the summarization of our comments before dissemination to ABRAC.

Respectfully submitted,

Peggy G. Lemaux, Ph.D.

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September 4, 1992

SUBJECT: Comments on questions raised by APHIS, ABRAC meeting, August 25, 1992

TO: David Andow

FROM: R. James Cook, Research Leader

The following comments are made as you requested as my responses to the questions raised by APHIS at the August 25, 1992, meeting of ABRAC.

Performance Standards for Safe Conduct of Field Tests

It is my opinion that the performance standard approach to the conduct of safe field tests with transgenic plants can be justified scientifically. Furthermore, I commend APHIS for taking steps toward performance standards as a means to facilitate field tests with transgenic plants. I would suggest, however, that the first performance standard may be the only performance standard needed to accomplish this goal. In fact, it is my opinion that if the first performance standard is met, all other performance standards become unnecessary if not moot or counterproductive.

The first performance standard states that "no plant pest or genes from a plant pest is involved in the genetic engineering except for any one or any combination of...(1) *Agrobacterium tumefaciens* ...disarmed...of all functional genes...,(2) noncoding cis-acting regulatory DNA elements...derived from plant pests such as cauliflower mosaic virus and *Agrobacterium tumefaciens*...,(3) virus coat protein genes...[and] (4) virus antisense genes....

This performance standard, if met, can be justified as sufficient by itself for safe conduct of the field test for the following reasons.

1. There has never been a serious plant pest risk posed by any of these specific or similar genetic constructs from plant pathogens engineered into plants. Plants with DNA from a plant pathogen could no more take on the pest status of that pathogen than they could take on the pest status of an insect pest or plant parasitic nematode if genes or other coding sequences from these pests were engineered into the plant. Moreover, if the concern is for a significant plant pest risk posed by DNA from a known plant pest, then APHIS might well have considered the FPPA as a means to review or regulate

plants with chromosomes or parts of chromosomes introduced from weedy relatives of crop plants as done by plant breeders for the past 30-40 years. Crop plants could conceivably take on pest status as weeds but not as plant pathogens.

2. Any injury to the plant itself, caused by DNA engineered from a plant pathogen into the plant, would constitute no significant plant pest risk to American agriculture since the damage would be limited to the plants in the researcher's plots. There is no need for federal oversight as a means to protect plants in researcher's plots from possible injury caused by DNA from a plant pathogen (equivalent of a genetic disease). The FPPA is intended to protect American agriculture against significant plant pest risks, but is not intended to protect individual plants or plant lines from pests or diseases in researcher's plots. The FPPA has never been used to protect plants against injury caused when individual plants or lines have been deliberately inoculated with pathogens, nematodes, or insect pests by researchers, and nor is it of concern as a significant plant pest risk if individual plants or plant lines show symptoms of genetic disease in plots since these will only be eliminated anyway.

3. There is no need for federal oversight as a means to prevent some plant breeder from releasing a cultivar having genes for expression of symptoms of crown gall or CaMV, for example, since such injury would be equivalent to a genetic disease and no such cultivar would ever seriously be proposed for release into commercial use.

4. There is no significant plant pest risk posed by either *A. tumefaciens* or CaMV in the crop plants proposed by APHIS for consideration under performance standards for field testing. Neither of these pathogens are epidemiologically important on potatoes, corn, or soybeans, for example. It is scientifically possible, based on the published literature, to identify those crop plants for which there might conceivably be a concern for development of crown gall or cauliflower mosaic, but even with these crop species, no serious plant pest risk would be posed to American agriculture as a consequence of DNA from these pathogens used to engineer the plants, for the reasons given in 1-3 above.

5. Plants engineered other than by use of DNA from a plant pathogen, e.g., DNA from another plant introduced by electroporation or biolistics, could meet this one performance standard since "no plant pest or genes from a plant pest is involved...."

Regarding the performance standards for handling, testing, and shipping plant materials, if the first-stated performance standard is met, there would be no significant plant pest risk posed to American agriculture

> if such plants or plant parts, for some reason, were <u>not</u> "handled and accounted for in such a way that the identity of all material is known;" or
>
> if, for some reason, the plants or plant materials were <u>not</u> "shipped in such a way that the material is unlikely to be accidentally spilled;" or

if, for some reason, the plants were "accidentally mixed with...plant materials which are subject to unknown subsequent uses;" or

if, as a rare event, genes movement occurred to "plants which are subject to unknown subsequent uses"; or

if, for some reason, plant material were to "remain viable [in the field] and volunteer in subsequent seasons. "

Each of the proposed performance standards on handling, testing and shipping plant materials for research purposes are or should already be part of good experimental practices. On the other hand, the possibility always exists for loss or spillage of planting material, inadvertent mixing, gene transfer, or plant material remaining to volunteer at the test site. Such occurrences might be of concern if these plants constituted a plant pest risk, but with no scientific basis for concluding that a plant pest risk exists, (based on the first performance standard) there is no scientific basis for making these as rigid performance standards for field testing of genetically engineered plants.

In fact, it would be my opinion that the proposed performance standards for handling, testing and shipping material of genetically engineered plants not only are unnecessary, they convey entirely the wrong conclusion about the safety of these plants and would therefore be counterproductive as formalized standards.

It would seem adequate for researchers simply to notify APHIS when field tests were underway or about to begin with genetically engineered plants that meet the first (only) performance standard. Tests with plants that could not meet the first performance standard might require consultation with APHIS if a courtesy permit seemed appropriate, or because of the working relationships developed by APHIS with the states (recognizing that some state governments expect federal oversight in lieu of state oversight), but not necessarily because such plants would constitute a plant pest risk.

Identification of traits that would present special concerns if introduced in various plant species

While there may well be traits that present special concerns if introduced into various plant species, it is my opinion that identification of such traits will be both difficult and counter productive to the development of crop cultivars for commercial uses. This opinion is based on the following points.

1. Mr. Medley makes reference to traits involving products derived from human pathogens. However, it would seem logical that these kinds of traits would not meet the performance standard discussed above (the first in Mr. Medley's list), and therefore would not go forward without a permit in any case.

2. There may be a tendency to consider traits for disease and pest resistance in crop plants as of special concern. Thus far, however, the major "safety" issue cited is the potential for selection of strains or biotypes of the pest with tolerance to the resistance trait and therefore able to attack the resistant line or cultivar. This is not a new issue, having been a problem since the beginning of plant breeding for disease and pest resistance. There is no scientific basis for singling out pest resistance traits engineered by rDNA technology as a safety concern while treating pest resistance introduced by older methods of plant breeding as not a safety concern. It would also not be appropriate for the federal government to impose regulatory oversight on the hundreds or thousands of new crop cultivars introduced into agricultural practice each year in the U.S. on the basis that their resistance traits may not hold up under pest pressures. Most plant breeders take into account the life expectancy of and hence how many years of crop security are provided by each new trait for pest or disease resistance.

3. The introduction of a new toxicant for pest or disease resistance might be singled out as of special concern and therefore subject to federal approvals. Again, toxicants produced by plants for pest or disease resistance is not a new issue. Some resistant cultivars produced by older techniques may well be resistant to pests because of a toxicant new to that crop species or to the ecosystem where that crop species will be grown. I would also be concerned about a trend towards "the more we know, the more it gets regulated." I make this observation based on an impression that the only traits likely to be identified as presenting a "special concern" would be those sufficiently characterized such that the gene is characterized and the gene product is known. It would also not be scientifically sound to consider the trait as a special safety concern if the gene for disease or pest resistance is characterized and the gene product (or mechanism of defense) is known, but not of concern if the gene is not characterized and the gene product (or mechanism of defense) is not known.

4. Herbicide resistance might be identified as a trait of special concern. Again, the only safety concern that has been identified for herbicide resistance is the potential for gene transfer to a weedy relative, which would confer herbicide resistance to that weed and thereby limit the effectiveness of the herbicide for control of the weed. However, herbicide resistance in weeds is already a problem, owing to the selection pressure imposed on weed populations by years of use of herbicides. The chances are many times greater that resistance will turn up naturally in a weed population because of overuse of the herbicide than because of gene transfer from a crop engineered to express herbicide resistance. Herbicide resistance traits must be managed carefully, by agronomists and farmers, but do not represent a new or special safety concern to justify federal oversight by APHIS.

5. Traits that might invite greater use of pesticides could be identified as traits of special concern. However, this would be counterproductive to the development of crop cultivars. For example, corn with the double-sweet gene in sweet corn requires greater use of fungicides to protect these seeds during germination in soil from *Pythium* damping off in the soil (*Pythium* attacks seeds rich in sugars). Since this trait could invite greater

use of fungicide, by the criterion established, it would be identified as a trait of special concern. There are thousands if not tens of thousands of such traits introduced into crop plants to meet producer or consumer demands and other performance characteristics of crop plants that would then come under federal oversight.

6. The dwarf genes introduced into wheat and rice, respectively, resulted in stiffer straw and a shift in the harvest index in favor of more grain to straw. Cultivars with these genes also invited greater use of fertilizers and pesticides. These genes are now in most of the worlds wheat and rice cultivars. It would not make sense to have brought the dwarf trait under federal oversight as a trait of special concern because it invited practices that have presented safety concerns.

7. Serious thought should be given before any trait is identified as a special safety concern for the simple reason that once in "jail," it would become very difficult if not impossible to get the trait cleared as no longer of special safety concern.

Importation of exotic viruses

Scientists conducting research with exotic viruses know, or should know, that a permit is required from APHIS under authority of the FPPA. It should not matter whether the virus was imported whole or as genomic fragments later assembled--research in the U.S. with any exotic pathogen requires a permit from APHIS.

On the other hand, international or interstate shipment of genomic fragments of exotic viruses should not require a permit, nor should a permit be necessary to work in the U.S. with a genomic fragment of a exotic virus. The permit would only be required to work with the whole/complete virus, whether imported/shipped whole or completed or assembled after receipt.

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Davis, California 95616

FAX Transmittal Sheet: Page 1 of (4) pages
FAX Number: (916) 752-1185
DATE: September 18, 1992

TO: Ms. Maryln Cordle
Office of Agricultural Biotechnology
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Washington, D.C. 20250-2200
FAX: (703) 235-4429

FROM: Raymond L. Rodriguez
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DELIVERY INSTRUCTIONS: ( ) Urgent (X) Routine

Dear Ms. Cordle:

Please convey my apology to Drs. Andow and Young for the delay in returning this report. Please let me know if I can be be of service to ABRAC in the future.

Best regards,

R L Rodriguez

UNIVERSITY OF CALIFORNIA, DAVIS

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September 18, 1992

Ms. Maryln Cordle
Office of Agricultural Biotechnology
Room 1001
Rosslyn Plaza East
Washington D.C. 20250-2200

Dear Ms. Cordle:

According to Dr. Young's instructions and the charge given me by the ABRAC—Risk Assessment Working Group, I am submitting the following evaluation of the performance standards for field testing of transgenic plants recently developed by APHIS (document #181). I would like to express my appreciation to the ABRAC—Risk Assessment Working Group for giving me the opportunity to participate in this important and timely discussion. I hope ABRAC and the Risk Assessment Working Group find my comments constructive and useful.

Summary

Sound and scientifically-based mechanisms for assessing new technologies like genetic engineering are essential for gaining public confidence and acceptance. Although the performance standards currently being developed by the Animal and Plant Health Inspection Service (APHIS) are a step in the right direction, their emphasis on regulated articles makes it difficult to justify them on scientific grounds. Since the performance standards exempt those transgenic plants originally used to define a "regulated article", it is essential that this term be redefined to focus on those transgenic plants with real or potential risk to the environment. This change will place the performance standards approach on a sound scientific footing and assure their effectiveness and acceptance by researchers and the public. By developing a more scientifically-based and flexible set of regulations, APHIS can help reduce the administrative burden on academic and industrial researchers and ensure that the United States will maintain its lead in the field of agricultural biotechnology.

I. The basis for defining transgenic plants as "regulated articles" (and hence the basis for the performance standard approach) is not based on sound scientific principles and should be revised:

Sound and scientifically-based mechanisms for assessing new technologies like genetic engineering are essential for gaining public confidence and acceptance. As public concern over the release of genetically engineered plants into the environment grew in the mid 1980's, APHIS responded by subsuming transgenic plants under the Federal Plant Pest Act of 1957. The basis for this decision was the presence, in transgenic plants, of DNA sequences related to plant pests (e.g., cauliflower mosaic virus promoter and T-DNA regions from the Ti plasmid). According to APHIS, the presence of such sequences in the transgenic plant defined it as a "regulated article"

and hence subject to regulation as a plant pest. This decision now requires investigators to apply for field trial permits to determine if their transgenic plants are hazardous to other plants or the environment. Since 1987, APHIS has issued over 300 such permits and to date, no transgenic plant has been found to be harmful to plants, animals or humans. The principal reason for this is that partial nucleotide sequences from the genomes of plant pests are incapable of conferring plant pest characteristics. Furthermore, the presence of these sequences can not substitute for the millions of years of evolution required to establish successful host-pathogen interactions. It is now clear to researchers and much of the informed public that plants modified by recombinant DNA technology, do not constitute plant pests *per se* nor is there reason to believe that they are capable of harming other plants in natural or managed ecosytems.

The term, "regulated article", represents a regulatory anomaly that places under the authority of the Federal Plant Pest Act, the process of plant genetic engineering as well as plant pests (-see page 238-9 of document #180). As a result, most transgenic plants, including those covered by the past 319 permits issued by APHIS, have been place into an unnecessary review process that hinders rather than stimulates the development and transfer of this important, new technology. APHIS points with pride to the fact that it now takes an average of less than 100 days to issue a permit as compared to the three years needed to approve field testing of the ice-minus bacterium. In almost every instance, the transgenic plants for which field testing permits were issued could have been evaluated by "prior notification" and using established field trail procedures for new plant varieties developed by conventional methods. Put another way, it could be said that the field testing of these transgenic plants was delayed for an average of 100 days for no reason other than they contain recombinant DNA sequences. Until the term regulated article is redefined to clarify and narrow its scope, it will be difficult to develop regulations and standards based on sound scientific principles.

II. Performance standards are a step in the right direction, but it is unclear what plants will be subject to these standards.

The development of performance standards by APHIS represents a positive step toward providing a uniform and scientifically-based set of standards for assessing the real or potential hazards of new plant varieties. However, for the reasons stated above, applying these standards to regulated articles, as they are currently defined, will undermine the effectiveness of these standards by coupling the process by which transgenic plants are created with legitimate concerns over the unintentional release of plant pests into the environment. Performance standards should be applied to *bona fide* plant pests (or to plants for which there is good reason to believe can act as plant pests) and not to regulated articles as they are currently defined.

What plants should be regulated? Some transgenic plants, particularly those expressing traits of special concern, will require careful assessment by field testing. Some examples include: (1) transgenic plants which utilize plant pests as hosts, (2) transgenic plants which utilize exotic plants as hosts, (3) transgenic plants in which the complete genome of a plant pest has been introduced, (4) transgenic plants in which the complete genome of an exotic plant virus has been introduced, (5) introducing a gene or gene combinations into the host plant that confer plant pest characteristics (e.g., weediness) and (6) introducing a gene or gene combinations into the host plant that change, in a fundamentally important way, the adaptive characteristics of the host (e.g, annual vs. perennial, self-crossing vs. out-crossing, enhanced selective advantage). The use of existing crop varieties to express pharmaceutical and therapeutic agents, immunologically reactive proteins and hydrocarbon polymers should not be placed in the latter category unless there is strong reason to believe that they constitute a real of potential hazard to the surrounding plants and animals.

III. Specific responses to the questions and points for discussed raised in document #181.

Question 1, Page 1 of Mr. Medley's letter to Alvin Young: Yes, the performance standard approach can be justified scientifically but only if it takes into account the wealth of information available on past field trials. Over the past several decades, hundreds of millions of genotypes have been field tested and over 300 transgenic plants have been or will be field tested in the next few years. This information should be used to develop "general principles" on which performance standards are based. For example, the recommendation of a one-quarter mile distance between transgenic potatoes and the nearest sexually receptive plants to prevent gene flow out of the test area, should be based on past experience and not arbitrarily defined.

There was some concern expression at the August 25th meeting, and in document #178, that "the opportunity to collect important data on environmental effects is not being fully realized". APHIS should make a concerted effort to derive as much information as possible from these field trials and apply this information to the development of performance standards.

Question 2, Page 1 of Mr. Medley's letter to Alvin Young: As a consequence of evaluating the results of past and present field trial, it may be possible to develop "generic" sets of performance standards. The development of these generic standards should evolve, however, as our understanding of how transgenic plants perform in the field increases. Because of the great diversity that exists in modern crop plants, it may not be possible to develop a single set of generic standards. Rather, generic standards for broad crop types should be developed.

Points for discussion: Mr. Medley submitted as points for discussion, a draft plan for performance standards to assess the risks of transgenic plants. With the caveats mentioned above, these standards should be helpful in establishing reasonable and uniform assessment procedures for the investigator. One aspect of these standards which received considerable discussion at the August 25th meeting was the issue of monitoring gene flow from transgenic plants to unrelated plants in the surrounding environment. This is an important issue and reliable data on gene flow will be invaluable in designing future field trials and in alleviating public concern about the spread of recombinant DNA sequences into the environment. However, a rigorous and meaningful analysis of gene flow is a complex matter and could represent an undue burden for the investigator. Furthermore, containment procedures such as the sexual isolation of transgenic plants is only one parameter to be tested in gene flow studies. The USDA should provide funds to support gene flow research that would provide the information needed to design effective performance standards for future field trial. Only through the use of regulations based on scientifically sound data will the public accept the products of plant biotechnology as safe and beneficial.

Sincerely yours,

Raymond L. Rodriguez

Raymond L. Rodriguez
Professor of Genetics

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FACSIMILE COVER LETTER

DATE: September 22, 1992

INCLUDING THIS COVER PAGE, THIS DOCUMENT CONSISTS OF 13 PAGES

DELIVER TO: Dr. David Andow
Dept. of Entomology
Univ. of Minnesota

FIRM OR DEPT. Fax #612-625-5299

COMMENTS: Pls find attached copy of my written comments to questions raised by the Animal and Plant Health Inspection Service per request from Mr. Alvin Young, ABRAC. The disc is also being mailed to you today.

SENDER: Robert T. Fraley
MONSANTO COMPANY
TELEPHONE #314-694-3925
FAX # 314-694-6888

IF YOU DO NOT RECEIVE ALL PAGES OF THIS TRANSMISSION, PLEASE CONTACT CAROL CRAIG AT 314-694-3925.

SCIENTIFIC ISSUES AND PRINCIPLES PERTAINING TO THE FIELD TESTING OF NEW PLANT LINES

In general, the concept of performance standards for safe conduct of tests is scientifically justified and suitable standards can be written based on the following considerations.

The major issues in the conduct of a test safe for the environment, wild life and humans are containment of the gene through control of the experimental crop and its propagules and of the experimental food/feed product. The appropriate actions to address both question are crop specific. Data on the disbursement of pollen and out crossing from various crops has been accumulated from years of experience in breeding. Recently, experiments have been conducted which demonstrate that the pollen or seed of transgenic crops maintain the same behavior as their non-transgenic counterparts (Dale et al., 1990, 1991; Crawley et al., 1991; Bing, 1990; Downey and Bing, 1990; Lowe, 1990).

The principle that performance standards are crop specific is recognized in the specific examples given in Dr. Medley's August 8, 1992 letter to ABRAC (#181). As example, the standards for field testing of potatoes depend on the biology of potatoes and these criteria provide appropriate containment to guarantee a trial that poses minimal risk independent of the gene tested. The isolation from other potatoes should ensure both containment of the genetic material and preserve the identity of the product (in this case tubers) so that experimental materials do not enter commerce prior to the assessment that a new potato variety would normally undergo. In the other examples, separation distances and segregation practices appropriate to the crop preserve the genetic and physical isolation required. The requirement for site monitoring to ensure that no material has remained in the field is appropriate and is dependent on the crop. The generic standards capture all of these points and are useful as points to consider in writing crop specific performance standards so that the scientist wishing to do a test has detailed

guidelines to follow in designing a test that will meet the standards.

The four categories of transformation systems or genes from plant pests that are designated for exception are also scientifically and empirically justified as discussed in the following. Specific references to literature citations are given and tables of data summarizing the numbers of transformants and various Monsanto field trials are also enclosed. The plants in the laboratory and field trials exhibited no properties other than those intended by the transformation and provide a large number of examples to support the conclusions that these techniques and genes do not lead to pest like qualities.

1) The safety and "non-pest nature" of plants generated using *Agrobacterium* with disarmed T-DNAs in either cointegrate or binary configurations are supported by a history of use. Transgenic plants of nearly 35 species (Gasser and Fraley, 1992) produced using *Agrobacterium* with disarmed T-DNA vectors have been reported with no description of any unusual properties. These observations have been extended to multi-site, multi year field trials for several of these species (tobacco, tomato, soybean, cotton, oil seed rape and sugar beet) again with no appearance of unusual properties resulting from the transformation system (Mackenzie. and Henry, 1990; Proceedings of the Second International Symposium on the Biosafety of Field Tests of Genetically Modified Plants and Microorganisms, Goslar, Germany. May 11-14, 1992; Huttner et al., 1992)

It is important to note that although the physical means of DNA transfer such as micro-projectile bombardment or electroporation are used to produce plants of several species including corn, rice and soybean. These methods have not been reported to produce unusual plants assayed under both laboratory and field conditions. These methods would, of course, not be regulated as plant pests

2) The exception of *cis*-acting regulatory DNA elements (promoters, terminators, enhancers, introns) derived from plant pests sources such as *Agrobacterium tumefaciens* T-DNA genes or plant viruses such as cauliflower mosaic virus (CaMV) is also more than supported by the same

history of use data. The transgenic plants described above carry introduced chimeric or composite genes that use regulatory elements derived from one or both of these sources to yield expression. It is clear that since these plants showed no unusual "pest like" characteristics, these genetic elements do not lead to "pestiness" (Mackenzie. and Henry, 1990; Proceedings of the Second International Symposium on the Biosafety of Field Tests of Genetically Modified Plants and Microorganisms, Goslar, Germany. May 11-14, 1992; Huttner et al., 1992; Table 1). This conclusion may be extended to similar elements from other plant DNA viruses such as other caulimoviruses (Gowda et al., 1989), BADNAviruses - pararetrovirus (Medberry et al., 1990), geminiviruses (Sunter and Bisaro, or other *Agrobacterium* sources such as the *rhizogenes* strains. The important criterion is that these segments do not produce a protein necessary for pathogenicity of the plant pest. DNA segments utilized for these elements are usually encoded in a few hundred nucleotides of completely sequenced DNA that do not encode such a protein. For new elements, this is predictable from the sequence. Further empirical evidence for the lack of "pestiness" can be ascertained from examination of plants in the laboratory growth chambers and greenhouse with little concern that unusual properties will appear in the field. Examination of a small number (10) of plants should provide more than sufficient data.

It is worth noting that most if not all of these transgenic crops with the exception of corn, were produced using the kanamycin resistant conferring neomycin phosphotransferase (NPT) gene to identify them. It is also worth noting that example plants of most if not all of these transgenic species have been made which carry the E. coli ß-glucuronidase (GUS; Jefferson, 1987) gene. No plants that produce either of these proteins have been reported to have pest qualities or any other unusual behavior (Table 1, Bijvoet and Nap, 1991; Flavell et al., 1992; The exception of DNA sequences that encode these proteins should also be standard practice.

(3) Exception of viral coat protein genes (Beachy et al., 1990) is justified based on the fact that the proteins produced by these genes do not appear to be determinants of pathogenicity as demonstrated by field trials of plants producing the coat proteins of tobacco mosaic virus (TMV; Nelson et al., 1988), tomato mosaic virus (TOMV), cucumber mosaic virus (CMV;

Cuozzo et al, 1988) , potato virus Y (PVY), potato virus X (PVX), potato leaf roll virus (PLRV), and alfalfa mosaic virus (AMV). None of these plants were reported to evidence unusual properties or pestiness. Once again it would be unlikely that production of a new viral coat protein would lead to unusual properties and this could easily be assayed by examination of a small number of plants in the laboratory setting.

Production of replicases would be unlikely to produce unusual properties. The replicase requires specific target RNA or DNA sequences to reproduce an RNA or DNA and sometimes accessory proteins, in addition. Full or partial replicase proteins from tobacco mosaic virus (TMV; Golemboski et al, 1990; Carr and Zaitlin, 1991; Ogawa et al, 1991), potato virus X (PVX; Braun and Hemenway, 1992), tomato mosaic virus (TGMV; Hanley-Bowdoin et al, 1990) and brome mosiac virus (BMV, Mori et al, 1992) have been produced in transgenic plants sometimes to quite high levels with no unusual properties evidenced. The RNA virus replicases share many common features (Koonin, 1991), once again it would be unlikely that production of a new viral replicase protein from the same class of virus would lead to unusual properties and this could easily be assayed by examination of a small number of plants in the laboratory setting.

4) Exception of antisense genes of viruses endemic in the US is also supported by the facts. Plants producing antisense of coat protein or replicase genes have been reported which exhibit unusual properties. Once again it would be unlikely that production of a new viral antisense RNA would lead to unusual properties and this could easily be assayed by examination of a small number of plants in the laboratory setting. Examples of viruses for which anti-sense has been applied are CMV (Rezaian et al, 1988), PVX (Hemenway et al, 1988) and tomato golden mosiac virus (TGMV; Buck and Hayes, 1991)

It is difficult to understand what would be the argument against including antisense genes to all endemic viruses in this exception.

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Table 1. Complete absence of disease symptoms in transgenic plants of various species under growth chamber, greenhouse or field conditions. All of these plants were produced at Monsanto (St. Louis) using disarmed Ti plasmid transformation systems and carry promoters or poly-adenylation sequences derived from plant pathogens. Kanamycin (NPT) or glyphosate tolerance were used as selectable markers except where noted.

Crop	Kanamycin	Glyphosate	Total	Disease Symp.
Canola	1000	2500	3,500	0
Corn	(1750 non-Kan/Gly)	3250	5,000	0
Cotton	2330	0	2,330	0
Potato	1500	2500	4,000	0
Soybeans	25	0	25	0
Tomato	9300	700	10,000	0
			24,855	0

MONSANTO USDA/APHIS FIELD RELEASE HISTORY

YEAR	CROP	TRAIT	# OF SITES
1987	Tomato	Insect Resistance	1
1987	Tomato	Virus Resistance	1
1987	Tomato	Glyphosate Tolerance	1
1988	Tomato	Insect Resistance	2
1988	Tomato	Virus Resistance	2
1988	Tomato	Glyphosate Tolerance	2
1989	Tomato	Insect Resistance	3
1989	Tomato	Virus Resistance	1
1989	Potato	Virus Resistance	2
1989	Cotton	Glyphosate Tolerance	2
1989	Cotton	Insect Resistance	1
1989	Soybean	Glyphosate Tolerance	4
1990	Tomato	Insect Resistance	2
1990	Tomato	Virus Resistance	1
1990	Cotton	Glyphosate Tolerance	4
1990	Cotton	Insect Resistance	10
1990	Potato	Virus Resistance	2
1990	Potato	Insect Resistance	1
1990	Soybean	Glyphosate Tolerance	17
1991	Tomato	Ripening	1
1991	Potato	Virus Resistance	5
1991	Potato	Insect Resistance	7
1991	Potato	High Solids	1
1991	Cotton	Insect Resistance	10
1991	Soybean	Glyphosate Tolerance	14
1991	Corn	Insect Resistance	1
1992	Corn	Glyphosate Tolerance	1
1992	Corn	Insect Resistance	1

1992	Cotton	Insect Resistance	23
1992	Cotton	Glyphosate Tolerance	1
1992	Potato	Insect Resistance	9
1992	Potato	Insect Resistance/Hi Solids	4
1992	Potato	Virus Resistance	5
1992	Potato	Insect/Virus Resistance	3
1992	Potato	High Solids	3
1992	Soybean	Glyphosate Tolerance	87
1992	Tomato	Ripening	3
1992	Tomato	Virus Resistance	1
1992	Tomato	Glyphosate Tolerance	1
1992	Tomato	Pyridine Tolerance	1
			241

MONSANTO USDA/APHIS FIELD RELEASE HISTORY

CROP	TRAIT	TOTAL NUMBER OF SITES 1987 - 1992
Tomato	Insect Resistance	8
Tomato	Virus Resistance	6
Tomato	Glyphosate Tolerance	4
Tomato	Pyridine Tolerance	1
Tomato	Ripening	4
		23
Potato	Virus Resistance	17
Potato	Insect Resistance	21 (3 with Virus Resist)
Potato	High Solids	4 (4 with Insect Resist)
		42
Cotton	Glyphosate Tolerance	7
Cotton	Insect Resistance	44
		51
Soybean	Glyphosate Tolerance	122
Corn	Insect Resistance	2
Corn	Glyphosate Tolerance	1
		3

Grand Total = 241 sites

S U N Y

THE COLL

Office of the Dean
JFT 614

Liberal Arts and Sciences
914-257-3520

September 16, 1992

David A. Andow, Ph.D.
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Dear David,

I am at a significant disadvantage in commenting on document 181 given that I was not part of the discussion. Furthermore, most of the issues are scientific issues even though their answers are not straightforward.

I have a few ideas on the performance standards question, but first a word on traits of special concern. For the reasons Fraley gave, this does not appear to be a promising approach. The relevant unit, from a safety point of view, is not the trait, but the trait-donor-recipient-environment complex. If performance standards are properly developed, a discussion of traits will come up in their relevant context.

I am confused as to exactly what "performance standards" are and how they are used. I will assume that they will be used to quickly tell whether an experiment should go ahead or not. Part of my confusion arises because of the alleged distinction between performance standards and design standards. I believe there is such a distinction, but I am not sure how useful it is. What will be useful are fairly general design standards. Consider the final sample performance standard--"The experiment should be conducted such that it poses no significant impacts..." This is an absolutely perfect performance standard, but one that is totally useless. The whole issue will be how we know the standard is met. On the other hand, take the first stated standard for soybeans--"No plant pest or genes from a plant pest is involved ... except for ..." This seems to be a design standard.

We want standards that are as general as possible but as epistemically obvious as possible. These criteria pull in

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different directions. At this point in our knowledge, useful (indisputable) standards will have to be crop specific.

Sincerely,

David

A. David Kline
Chair, ABRAC
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5 September 1992

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Dear David,

Here are my comments on the request and questions from APHIS regarding document ABRAC #181.

1. Can the performance standard approach be justified scientifically?

It is not completely clear what is implied by this question, but there are certain aspects of this approach that could be standardized. Alternatively, it would not be justified to use a single set of performance standards in all cases.

2. How to do this?

Performance standards need a more specific framework. I suggest that they begin on a crop by crop basis and use the general framework of our ABRAC guidelines to define containment standards for specific categories that we have previously defined. It should be easy and appropriate to define performance standards for specific typews of experiments with specific types or groups of crops.

To make performance standards scientifically based, the ABRAC guidelines are a simple format to use. Any group of crops and modifications that have the same biological properties and the same level of risk could easily be justified to use the same performance standards.

Performance standards could be used on a trait basis if it were clear that a particular trait posed no risk in any plant under any circumstances. Again the ABRAC guidelines are a guide to evaluate risk from traits. For

neutral traits, simple standard agricultural practice should be adequate but the perceived risk is not independent of the crop. In one case, such as maize, the gene could never "escape" but for other crops with weedy relatives, genes could enter the natural environment..

3. What type of data are needed?

The key to the question is the matching of containment with risk. If the re are different levels of risk, ther must be different levels of containment. To apply one standard to all cases would be either wasteful or dangerous. Where data are needed, they are concerned with unknown risks of specific plants with known genes, and the lack of data on the possiblity of release, or escape of genes into the natural environment.

TRAITS OF SPECIAL CONCERN:

Again the ABRAC guidelines should be examined to determine what traits or classes of traits are of concern and how to approach evaluation for performance standards. Characteristics of the unmodified plant are of primary concern, followed by the characteristics of the gene, and the results of specific modification. Again the guidelines are designed to make these kinds of evaluations.

IMPORTATION OF EXOTIC PLANT VIRUSES:

There are two issues here. One is how to safely transport exotic viruses. The other is whether people should be allowed to work with them and what containment should be allowed. First, transportation as parts of viruses in DNA clones is extremely safe. As I mentioned, when sequence is know, small viruses ccould actually be reconstructed from sequence.

However, the risks of working with a natural exotic pathogen can be very great in the absence of adequate containment. And that should be regulated in some way. The problem here is regulation and containment. It should not be permitted for someone to recreate a dangerous virus without proper containment and without approval. Simply regulating transportation is not an adequate strategy anymore.

SOME OTHER ISSUES:

Use of disarmed Agrobacterium for transfer of genes, should be considered safe and should not be considered pathogenic or part of a pest or pathogen. Considering that the genes for pathogenicity are removed, and that even these are likely to have been derived from plants themselves, it seems innapropriate to continue this level of concern in

view of five years of field tests that show no pathogenicity. It was firmly predicted that there should be no pathogenicity, and now it can be demonstrated that there was none.

Well characterized regulatory elements should not be regulated even if they were derived from a pathogen. None of these elements has shown any properties that are different from endogenous regulatory elements. As soon as these elements are sequenced and tested in several divergent test systems, they should be deregulated. It is most unlikely that a regulatory element alone will confer pathogenicity or risk to health or to the environment. The regulated elements from CaMV (35S promoter) and AGrobacterium (nos terminator) are well defined, do not have properties that should distinguish them from endogenous plant regulatory sequences, and therefore they should not be regulated articles.

Antisense elements for endogenous genes are likely to occur as natural mutations by inversions and therefore are unlikely to pose risks as engineered constructs, that are different from risks due to mutations that occur frequently in unmodified crop plants.

Sterility is only one aspect of containment. Containment must be appropriate for the plant, genes, climate, and ecological environment. Wherever sterility can be engineered into a plant, it would of course aid in containment.

Viral coat protein genes and other genes, should not be considered pathogenic under conditions where normal plants have been regularly exposed to the normal virus. The introduction of a single gene from the virus is not likely to pose any risk compared to the risks of gene transfer that occur during normal plant infection.

I think that covers the major questions and issues raised that I could constructively comment on.

Sincerely,

Ron Sederoff

National Audubon Society

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September 10, 1992

Dr. David Andow
University of Minnesota
219 Hodson Hall
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Dear David:

I have enclosed a disk and hard copy of my comments on the APHIS paper. I have made some minor changes from the version Ifaxed to you.

The disk is formatted for PC. I saved the file in MicroSoft Word format, and also as ASCII. One of these should work for you.

Hope all is well.

Sincerely,

Ed

Edward Bruggemann, Ph.D.
Staff Scientist

Performance Standards

1. Can the performance standard approach be justified scientifically?

In principle this appears to be a reasonable approach for APHIS to take. However, I remain concerned about the implementation and enforcement of the performance standards. I do not agree that "scientific" consideration of the performance standards can be usefully divorced from provisions to insure compliance with them.

2. If this approach is valid, what is the most appropriate way to describe such performance standards? Should performance standards be described as a single, generic set of standards or should they be tailored specifically to individual crops?

Generic performance standards are at this point not appropriate. In particular, the fourth generic performance standard ("The experiment should be conducted such that it poses no significant impacts on populations of flora and fauna beyond the temporal and geographic bounds of the field test. This should include the environmental fate of the transgenic plant.") is an admirable statement of principle but it is so broad, vague, and offers so little guidance that it is not useful. Specific environmental hazards and specific "significant impacts" posed by specific transgenic crops should be addressed in the performance standards.

3. What type of data would confirm that the presumption of safety was correct?

Field data from experiments designed to test hypotheses concerning specific environmental effects. Appropriate statistical analysis would allow some statement of certainty or confidence in the conclusions.

Traits of Special Concern

1. Can criteria be developed for determining what traits or classes of traits should be of greatest concern if introduced into plants?

I am not sure that criteria could be developed that would fully anticipate future innovations in plant biotechnology. Consequently, I am reluctant to establish such criteria. On the other hand, the examples provided in the letter from APHIS do illustrate some traits that, in my opinion, clearly raise special concerns and they should be treated as such. Manufacture of pharmaceutical and therapeutic agents in transgenic plants is an obvious candidate for trait of special concern. For that matter, any biologically active product intended for human or veterinary use but not naturally found in the parent plant should be considered a trait of special concern. Products derived from human or animal pathogens should also be

considered traits of special concern, especially if the traits are toxins or if they are implicated in pathogensis.

2. What characteristics of the plant's biology will be of relevance in asssessing potetial risks?

The potential for any person or animal to injest, absorb, inhale, or otherwise be exposed to the products described above must be evaluated. Both the transgenic plants and the transgenes must be rigorously controlled. If the parent plant is a crop plant used for food, feed, or forage, or is related to such a crop plant so that cross-pollination can occur, the risks are obvious. However, all potential uses of the parent plant and its relatives by humans and animals, both domestic and wild, as well as the means for dispersal and potential to persist must be considered.

Importation of Exotic Plant Viruses

1. What criteria should be used in evaluating the risks associated with the importation of portions of viral genomes?

2. What biological attributes of the virus and host plant will be necessary to safeguard the health of other plants?

Importation of plant viruses that do not now occur in the US may pose significant risks. New developments in biotechnology have provided the incentive and means for researchers to import these viruses. The basic question is whether any of these viruses should be admitted into the US for research purposes. For some viruses the risks posed by the virus may be too great to justify importation for any reason. For other viruses, appropriate containment conditions for research may reduce the risks so that the importation may be allowed. Perhaps some exotic viruses pose low risk because there are no suitable hosts or vectors in the US.

In answer to the first quesion, I believe that the risk posed by the virus itself should be the primary consideration. Because viruses can be reconstructed from the viral genome, and because viruses can be constructed from synthetic DNA (at least in principle), APHIS should seek some means to oversee and regulate these activities. Exotic viruses constructed or reconstructed by these means pose identical risks to imported, exotic viruses.

However, I believe that the larger questions posed here are difficult for ABRAC to answer with authority. APHIS should formally consult with the professional, scientific community that has extensive expertise with viruses to determine the answers to these questions. It would be appropriate for the American Phytopathological Society (and other such organizations) to evaluate, in a comprehensive manner, the risks posed by exotic viruses. One result from this effort could be lists of plant viruses and

the conditions, if any, under which importation and research of these viruses could be considered safe. This information should be very useful to APHIS.

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September 28, 1992

To: Maryln Cordle

From: David Andow

Re: My comments on document 181

Attached are my comments to document 181. including this page, there are 8 pages. Please forward a FAX to Terry Medley or John Fayne, because I will not be able to do this for a couple of days.

Thanks for your patience. I caught a cold and was delayed in getting most of my work done.

Performance Standards and the Identification of Safe Experiments

David A. Andow
Department of Entomology
University of Minnesota

Can the performance standard approach be justified scientifically?

Although I am still unclear as to the precise nature of 'performance standards,' I think that it is possible to identify categories of experiments that can be considered safe. In general, these categories must be based on:

- the materials used in the experiment (for example, including, but not necessarily limited to the parent plant and the particular phenotypic modification),
- the geographic locality of the experiment, and
- the level of safeguards followed during the performance of the experiment.

From my examination of document 181, the 'performance standards' proposed by APHIS rely on these elements, so I believe that the approach used by APHIS can be justified scientifically.

I believe, however, that a scientifically justifiable process by which one could identify these categories has not been presented to or developed by the Working Group, and this concerns me. Therefore, I am unable to concur that the proposals suggested in document 181 are the most appropriate way to approach these standards, nor can I concur that the particular proposals have been justified adequately and scientifically. In what follows, I will clarify this opinion. I will address many of the questions in document 181 indirectly in what follows, but my omission of comment on any particular question should not be taken to imply any particular opinion on the question.

I do agree with the overall procedural strategy pursued by APHIS to ensure environmental safety. It is my understanding that APHIS is approaching the regulation of these experiments with a presumption of risk, making it necessary to develop scientifically justifiable arguments to exclude some of the experiments from this presumption of risk and conclude that they are presumably safe. By safe, I mean that the experiment can and should be conducted under normal agricultural research practices. I would be willing to provide a scientific rationale for this position if it seems necessary.

In addition, I agree with the types of environmental safety issues that APHIS has identified. Specifically they recognize both direct plant pest risk and indirect plant pest risk. A direct plant pest risk is one in which the regulatable organism might cause injury directly to a plant. If prior to genetic transformation, the regulatable organism was not a direct plant pest, and the trait being transferred was not from a plant pest and

the regulatable organism itself exhibited no characteristics similar to those exhibited by plants being affected by a plant pest, then it seems appropriate to conclude that the regulatable organism poses no direct plant pest risk. Indirect plant pest risk, however, will require considerably greater levels of investigation Such indirect effects include, but are not limited to, spread of herbicide resistance to agricultural weeds which threaten other agricultural crop plants, consumption of pharmacologically active compounds by wildlife which induces them to eat or damage greater quantities of other plants, evolution of resistance to specific plant toxins by arthropods which extends the host range of these arthropods and allows them to become pests of other plants. While it is certainly not true that any of these scenarios have been realized with particular genetically engineered plants, these examples strongly suggest that there are many indirect plant pest risks that require a sophisticated system of oversight.

I commend APHIS for their use of these two points and on their continuing effort to revise their regulatory standards.

The central procedural concern that I have is how to marshall and present the various types of scientific evidence to build a credible scientific case to justify particular 'performance standards.' Within document 181, I have identified at least five different types of scientific inferences. In addition, I discuss four more that were not addressed explicitly.

o The first I will call 'safe experimental repetition inference,' or the most scientifically conservative inference. If an individual or organization desires to repeat an experiment at a different time, and that experiment has already received a permit for experimental release from APHIS, then it is not necessary for APHIS to examine this repeat proposal as intensively as the first proposal This inference is scientifically conservative because it proceeds as if scientific generalizations are likely to be highly particular and restricted to specific organisms, traits, and localities.

  This inference can be justified on the grounds that the experiments are strictly identical. APHIS, in issuing the first permit, had decided that the first experiment would be safe. Additionally, APHIS presumably has received some data from the first applicant demonstrating that the experiment was conducted and that it was safe. Therefore, under the assumption that temporal variation in the local environment is not expected to cause the occurrence of any unforeseen events, it can be inferred that a repetition of the experiment should also be safe. Clearly, the assumption that temporal variation in the local environment will not cause unforeseen events should be considered. There is reasonable evidence that the success of a species invasion can be mitigated by temporal variation in the local environment, so the assumption cannot be considered valid in all cases. In many

of the cases proposed by APHIS, it is very unlikely that temporal variation in the environment is likely to influence the potential effects of the plants on the environment.

- The second is the 'safe vector inference.' One particular example proposed by APHIS is the presumptive safety of *Agrobacterium tumifaciens* vectors that have had all functional genes occurring on the T-DNA removed. As justification for this position, APHIS and many members of the Working Group cite the occurrence of over 100 field trials with plants transformed by this vector, none of which have exhibited direct or indirect plant pest risk. This is an argument by induction, and historically, argument by induction has never been deemed an reliable method of scientific proof. For example, if we were to look at the Red Baron's dogfight dueling record after 50 duels, by pure induction we would infer that he was unbeatable, which is clearly a ludicrous assertion. For the cases with which we are concerned, risk is low, which further limits inductive arguments. For example, if I were to drive my Corvair or Pinto on 1000 trips and not have an accident, does this imply that my car is safe? Clearly it is necessary to couple inductive arguments with deductive arguments that are based on accepted biological principles and several independent ancillary observations. When this is done, very compelling scientific arguments can be constructed. These arguments would include, among many other points, how it is known and how it can be ensured that all functional genes have been removed from the T-DNA. Because these arguments have not yet been presented, I am unwilling to accept the conclusion that there is a safe vector system.

  The relationship between observation and inference, however, is considerably more subtle than this. As just mentioned, an argument can be created that supports the position that a specific vector is safe by marshalling general theoretical arguments and specific empirical observations. This, however, is a conservative scientific argument, implicitly accepting the concept that scientific generalization is likely to be limited to specific vector systems. In reality, most scientists would entertain the idea that classes of vectors might be argued to be safe. For example, not only crown gall vectors, but cauliflower mosaic virus vectors and other viral vectors can be considered safe. To make this argument, one must identify the specific characteristics of these vectors that make them safe, generate an argument of the form: (1) these characters make any vector with the characters safe, and (2) there are no exceptions to rule (1). I have not heard or read any of these arguments formally presented, and without such a presentation, I am unable to accept that there is a category of vectors that are safe. Despite my agnostic position, I believe that it will be possible to develop such arguments.

- The third, fourth and fifth are 'safe trait inferences.' The approach presented to the Working Group is to consider each trait individually for a particular crop plant

species in a circumscribed geographic region. In general, this seems appropriate, because there is too little information to allow for a broader treatment of large categories of traits. If this approach is considered valid (and I think that it can be justified scientifically), an additional implication is that it will be possible to identify 'traits that require review' for particular crop plants in a circumscribed geographic region.

Three types of traits might be considered for 'safe trait inferences:' "marker genes," non-coding *cis*-acting regulatory DNA elements derived from plant pests, and virus resistance genes, using either viral coat protein genes or virus antisense genes. In general, inferences of environmental safety for these categories suffer from the same limitations as those 'safe vector inferences' discussed above. Thus, given the current presentation of the evidence, I am not prepared to conclude that any of these categories are safe.

In addition to this general concern, each of these types of traits raises specific safety concerns. "Marker genes" code for products that have no functional significance to the organism. For these, standards of evidence must be established that provide a convincing scientific case that the gene products have no functional significance. In principle, this may appear to be an impossible task, but I think that in specific cases it will be possible. For example, luciferase genes in most plants might be argued convincingly to have no functional significance to a plant. To date, such an argument has not been advanced.

The safety considerations of non-coding *cis*-acting regulatory DNA elements derived from plant pests present similar concerns. As with "marker genes," definitions of 'non-coding' and 'regulatory' must be made scientifically operational. An additional, special concern relates to the stability of the genome of the recipient plant. If the plant is known to possess transposable elements, such as corn, then a different and more elaborate scientific argument is required to justify the safety of these genetically engineered plants than if the plant is not known to have transposable elements. In the latter case, the evidence that the plant has no transposable elements should also be used to justify safety.

Genetic elements that code for gene products that are functionally significant for the plant are all discussed together here for convenience, but this does not imply that they can or should be treated together in performance standards. A general issue, which has been discussed in specific terms in the examples above, is that scientific criteria for establishing the absence of pleiotropic effects must be developed so that the scope of the discussion of safety considerations for traits can be suitably circumscribed. An additional issue, which I have alluded to above, concerns the scope of traits that are encompassed by the scientific inference of safety. For

example, there has been a significant amount of research done on potatoes that have been genetically engineered to express potato virus Y resistance, but no experimental field work on potatoes expressing potato virus M resistance. A scientific case has not yet been elaborated that indicates how previous experience with PVY-resistance can be used to justify the safety of PVM-resistance. Clearly, criteria for the extension of the scope of scientific inference from field test data are of considerable importance for streamlining the regulation of genetically engineered plants. It is these extensions of scope that are the heart and soul of scientific inference.

- The sixth is a 'safe crop inference.' This has not been proposed by APHIS, but is conceivably possible. Here, one might argue that for a suitably circumscribed geographic region, all genetically engineered traits of a particular crop are safe. This is clearly not the case, as illustrated by the examples that APHIS has presented under the category 'traits of special concern.'

  More restricted 'safe crop inferences' might be developed around a limited set of traits. For example, if the crop cannot overwinter, cannot outcross with any uncultivated plant species in the region, or both, then it has some level of biological containment, and many traits in such crops might be considered safe. Indeed, under this argument, crops for which no genetic engineering has been considered could be considered safe for field tests with a large number of potential traits. Clearly, the criteria by which it is known that a crop cannot overwinter or cannot outcross with uncultivated plant species must be clarified explicitly before this kind of argument can be defended. This type of inference, however, would be far more flexible than most of those that have already been proposed, and could link mitigation standards more closely with potential risk.

- The seventh are 'safe geographic region inferences.' Although this is not explicitly mentioned by APHIS, it seems to underlie much of their reasoning. That is, it is possible to identify regions in which experimentation with particular crop-trait combinations can be considered safe. Given that the entire geographic region that is to be protected from adverse environmental impact is only the United States, this is possible to accomplish. This issue is discussed further below outside of the context of current US regulatory policy.

- The eighth type are 'safe mitigation procedure inferences.' These are form the basis of many of the specific procedures proposed by APHIS for handling the genetically engineered crop plants before, during, and after the experiment. The idea is that mitigation performance standards can be developed to ensure the safe conduct of small field trials. In general, these standards are necessary, because it cannot be assumed that for any trait combined with a given crop, the field test will be safe. Thus, mitigation standards will be necessary. However, it seems to me that the level

of mitigation could be made a function of the level of risk. As the performance standards are now drafted, if the genetically engineered plant and trait arise in any way that does not connect them with the genome of a plant pest, then the only standards to ensure safety are the mitigation procedures (particularly for corn and soybean, but potato is also in this category because the amount of additional genetic material from other species is not well characterized). This seems both overly restrictive and overly permissive.

- The ninth type are 'safe source inferences.' I am not sure if these have been addressed adequately elsewhere, but it seems reasonably clear that if the source of the genetic material moved into a particular crop is that same crop species, then the genetically engineered crop plant should be considered safe. In addition, it should be possible to characterize the average proportion of the genome of a specific crop plant that is likely to have originated from uncultivated plants with which it can interbreed. This level, or one very close to this level, could be used as the proportion of allowable foreign genetic material in a genetically engineered plant that originated from a plant with which the recipient crop plant can interbreed.

In addition to this central concern about the establishment of a scientifically justifiable process to support arguments of environmental safety, I have several concerns that extend beyond the scope of document 181. The geographic scope of the US regulatory policy on biotechnology covers only the United States. Yet it is conceivable that some experiments that would be deemed safe in the US could use organisms that could disperse to foreign countries and cause adverse effects in those countries. I think that APHIS should be sensitive to this concern, yet I am not sure how to devise an effective policy. Two ideas might be to pay particular attention to crops with "wild relatives" in nearby countries and experiments conducted near those countries, or to pay particular attention to bird dispersed crops that fruit during the major migratory period of the local avian fauna.

In addition, I am concerned that the regulatory changes proposed by APHIS are focused overly on the major crops, such as corn and soybeans (and potato and cotton). Assuming that biotechnology will improve agricultural technologies, this regulatory policy has the effect of accelerating the concentration of agriculture in the United States to an increasingly homogeneous agriculture. This might increase the vulnerability of US agriculture to external environmental perturbation and further destabilize the already weakened social basis of agriculture.

As a consequence, I am concerned that APHIS should begin to consider some more difficult cases. For example, can performance standards be developed for plants that can overwinter (e.g., alfalfa, trees, etc.) or that can outcross with uncultivated species (e.g., canola, sunflower, etc.).

In summary, I believe that the efforts exhibited by APHIS to streamline their regulatory process are useful and appropriate. I can not concur that any of the specific proposals in document 181 have been justified scientifically. I do agree, however, that a scientifically justifiable process can be established that will produce the scientific justification for many of the specific issues proposed by APHIS.

Sincerely,

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